Hyponatremia: Epidemiology

- 15% of hospitalized patients
- Serum sodium of <130 mEq/L
  - Incidence of 1% and prevalence of 2.5%
  - 67% of cases were hospital acquired

Settings
- ICU 30%
- SAH 30%
- TBI 12%
- CHF 28%
- HIV 30%

Risk of Hyponatremia Increases with Age


Hyponatremia in the Elderly

- Overall incidence of [Na⁺] < 137 mmol/L ~ 7% ¹
- Prevalence increases to 18-22% in chronic care facilities, with 53% incidence of one or more episodes of hyponatremia ²,³
- Mortality rate = 16% for patients over 65 with hyponatremia versus 8% for those without hyponatremia on admission ⁴

Relationship Between Hospital Admission Serum [Na\textsuperscript{+}] and In-hospital Mortality

![Graph showing the relationship between admission serum Na\textsuperscript{+} concentration and predicted probability of in-hospital mortality.]


Hyponatremia and Mortality

![Bar chart showing mortality rates for hyponatremic and normonatremic patients.]

Mortality Rates are Uniformly Higher in Hyponatremic Patients with a Variety of Different Illnesses

- Heart failure: n = 397 (Flear)
- Pulmonary tuberculosis: n = 169 (Westwater)
- Child diarrhea: n = 1,330 (Samadi)
- Myocardial infarction: n = 153 (Flear)

Hyponatremia and Survival in Congestive Heart Failure (CHF)

Hyponatremia in Cirrhosis
Impact on Survival

![Graph showing the relationship between serum sodium concentration and the relative risk of death.]

Figure 1. Serum Sodium Concentration and the Relative Risk of Death after Adjustment for the MELD Score.


Neurohypophysis

- Arginine vasopressin (AVP) secreting neurons in SON and PVN
- Osmo- and thirst receptors/centers in anterior hypothalamus
- Ascending pathways from ANS and brainstem
- Terminal boutons in neurohypophysis
### Relationship between Plasma Osmolarity and AVP

![Graph showing the relationship between plasma osmolality and plasma AVP levels.](image)

#### Arginine Vasopressin (AVP) Receptors

<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>LOCATION</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1A</td>
<td>Vascular smooth muscle, platelets</td>
<td>Vasoconstriction, platelet aggregation</td>
</tr>
<tr>
<td>V1B</td>
<td>Anterior pituitary</td>
<td>ACTH release</td>
</tr>
<tr>
<td>V2</td>
<td>Renal collecting duct cells</td>
<td>Free water absorption</td>
</tr>
</tbody>
</table>
Aquaporins


Relationship between Urine Osmolarity and AVP
Hyponatremia: One of Many Algorithms

Clinical Features of CSW and SIADH

<table>
<thead>
<tr>
<th></th>
<th>CSW</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF*</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma albumin concentration</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma BUN/creatinine</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Plasma [K+]</td>
<td>Normal or increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma uric acid</td>
<td>Normal or decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Treatment</td>
<td>Normal saline</td>
<td>Fluid restriction</td>
</tr>
</tbody>
</table>

* Determination of ECF is the primary way to differentiate CSW from SIADH.

BUN=blood urea nitrogen; CSW=cerebral salt wasting.


Unifying Hypothesis of Sodium and Water Dysregulation After SAH

ECF=extracellular fluid; GFR=glomerular filtration rate.

Hyponatremia

- Disorders or processes that cause hyponatremia are dynamic:
  - Initiation
  - Maintenance
  - Recovery

- It is critical to ascertain where the patient might be in their course as one initiates and measures a response to management

Hyponatremia: Symptoms and Signs

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>71</td>
</tr>
<tr>
<td>Delirium/Confusion</td>
<td>50</td>
</tr>
<tr>
<td>Weakness</td>
<td>50</td>
</tr>
<tr>
<td>Lethargy</td>
<td>50</td>
</tr>
<tr>
<td>Myalgia/Cramps</td>
<td>21</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
</tr>
<tr>
<td>Hiccups</td>
<td>14</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>14</td>
</tr>
</tbody>
</table>

Headache!!!
Correction of Hyponatremia Normalizes Gait Stability in “Asymptomatic” Hyponatremia

serum [Na\(^+\)] = 130 mEq/L

serum [Na\(^+\)] = 139 mEq/L

serum [Na\(^+\)] = 124 mEq/L

serum [Na\(^+\)] = 135 mEq/L


Severe Hyponatremia
168 patients Na+ <115 mEq/L

Treatments for Hyponatremia

- Isotonic saline infusion
- Hypertonic saline infusion
- Vaptans: conivaptan, tolvaptan

- Fluid restriction
- Demeclocycline
- Furosemide + NaCl
- Mineralocorticoids
- Urea
- Vaptans: tolvaptan

Judicious use of 3% Saline

- Hyponatremic patients with significant neurological symptoms, such as seizures, severe altered mental status, or coma.
- The high likelihood of cerebral edema outweighs the risk of possible demyelination.
- Target rate of correction is 1.5 to 2 mEq/L per hour with 3% hypertonic saline for the **first 3 to 4 hours**, or more briefly, if symptoms improve or the sodium level exceeds 120 mEq/L.
Formula for Estimating Sodium Needs

3% Saline: An Alternative Approach

- Rate in mL/h is the desired rate of rise in Na+ in mEq/L/h per kg body weight.
- Furosemide 20 mg iv.
- For a 70 kg patient with desired correction rate of 1.5 mEq/L 3% saline infusion rate would be 105 mL/h.
## Fluid Restriction

### Vasopressin Receptor Antagonists

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>RECEPTOR</th>
<th>EFFECTIVE DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan</td>
<td>IV/Oral</td>
<td>V1/V2</td>
<td>20-40 mg/d</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Oral</td>
<td>V2</td>
<td>15-60 mg/d</td>
</tr>
</tbody>
</table>

Conivaptan IV

8-10% experience rapid correction

SALT 1 and 2: Mean Sodium Concentration Over Time


Hyponatremia

Hyponatremia: Outcomes of Correction


Osmotic Demyelination

Central Pontine Myelinolysis
Central Demyelination Syndrome
Central Demyelination

- Demyelination injury to oligodendrocytes
- Disruption of blood brain barrier may play a role
- Accumulation of microglial cells
- Release of pro-inflammatory cytokines
- Destruction of myelin
- Animal studies suggest minocycline and lovastatin may be protective
Clinical Features of Osmotic Demyelination

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutism/Dysarthria</td>
<td>71</td>
</tr>
<tr>
<td>Lethargy/Obtundation</td>
<td>57</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>29</td>
</tr>
<tr>
<td>Confusion</td>
<td>21</td>
</tr>
<tr>
<td>Movement difficulty</td>
<td>21</td>
</tr>
<tr>
<td>Muscle contractions</td>
<td>7</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>7</td>
</tr>
</tbody>
</table>

Spasticity, rigidity, Babinski reflex, hyperreflexia, impaired gag reflex, fasciculations, nonreactive or dilated pupils, snout, grasp or rooting reflexes, impaired gait, ataxia, cognitive deficits.


Reducing Risks of Myelinolysis

- Limit correction of chronic hyponatremia to 10 to 12 mmol/L in 24 hours and to 18 mmol/L in 48 hours.
- When other recognized risk factors for myelinolysis are present (menstruant women, hypokalemia, liver disease, poor nutritional state, alcoholism, burns), correction should not exceed 10 mEq/L/24h.
- In acute hyponatremia a more rapid initial correction rate, roughly 1-2 mEq/L, is acceptable.
Mismanagement of Hyponatremia

- 104 patients with Na+ <125 mEq/L in a 6 month period
- 42% of diagnoses incorrect
- 33% of patients with significant management errors
- Overall mortality 27%
  - 41% in those with errors in management
  - 20% in those managed appropriately


Hyponatremia
The Endocrinologists Role

- Understand the epidemiology and pathophysiology of hyponatremia
- Devise a systematic approach to the evaluation of patients with hyponatremia
- Individualize therapy based on pathophysiology
- Educate colleagues and trainees
  - Consultations
  - Grand Rounds and other presentations
  - Discussions